REMARKS

Applicant respectfully requests reconsideration. Claims 1, 8-13, 20-33 and 35 were previously pending in this application. No claims are amended herein. As a result, claims 1, 8-13, 20-33 and 35 are still pending for examination with claim 1 being an independent claim. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 1, 8-13, 20-33 and 35 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. More specifically, the Examiner argued that "the disclosure fails to provide sufficient guidance pertaining to the structural requirements of any given ISS-ODN" (Office Action page 2). Applicant respectfully disagrees for the following reasons.

The claims are directed toward methods for the induction of antigen-specific immune responses in a subject through the administration of antigen and a combination of adjuvants comprising a CpG dinucleotide and another non-nucleic acid adjuvant, such as PCPP polymer, LPS derivatives and MPL. The claims also include the limitation that the CpG oligonucleotide is 8-100 nucleotides in length and contains at least one phosphorothioate backbone modification. According to the Examiner, the specification fails to teach the skilled artisan sufficient guidance as to the flanking sequences, length, and backbone modifications of a CpG oligonucleotide to practice the claimed methods. The Examiner's position appears to be based on the notion that "[t]he state-of-the-art clearly demonstrates that flanking sequences, as well as backbone modifications can effect [*sic.*] the adjuvant activities of any given CpG-containing oligonucleotide in an unpredictable manner" (Office action page 2). In support of his position, the Examiner cited several articles pertaining to effects of flanking sequences and backbone modifications of CpG ODNs on immunostimulatory properties. Each of these references is briefly discussed below.

Hsieh et al. (Vaccine, 22:655-9., 2004) examined whether addition of CpG to a CFP subunit vaccine would increase resistance to a subsequent challenge with an infectious agent in the murine model of tuberculosis, *M. tuberculosis* (H37Rv strain). The authors employed a single CpG-containing ODN ("ODN 1826") for their experiments. The authors report two main sets of data: first, the authors observed that addition of CpG ODN to the subunit vaccine increased local IFNγ production as shown by ELISA. Second, the authors noted that addition of CpG to the subunit vaccine did not enhance protective immunity in the lungs of the infected mice.

It should be noted, however, that the results of Hsieh et al could be due to a number of issues related to their experimental protocol. For instance, Hsieh et al. provided a large challenge dose. The dose may have been too large. Additionally Hsieh et al tested only one antigen in their experiments. A more appropriate antigen could be identified by a skilled artisan by reviewing the available literature or performing routine testing. Thus, the authors' conclusion that "addition of CpG to the subunit vaccine did not enhance protective immunity in the lungs" of the infected mice must be interpreted in the narrow scope of their study. To conclude that CpG oligonucleotides are ineffective as a combination vaccine adjuvant, merely based on a set of experiments that used one antigen and no other optimization at all, is unreasonable. Indeed, the authors themselves considered their experimental model to possibly be flawed in the Discussion of the article (pages 658-9). Specifically, citing two earlier reports that showed positive effects of CpG as a vaccine adjuvants, the authors noted that "CpG motifs are immunostimulatory and several reports have observed positive effects as vaccine adjuvants…In both cases, however, the infectious challenge was given soon after, and it may be possible that the delay prior to infectious challenge in our study was sufficient to allow any possible effects of the CpG to subside" (pages 658-9). The authors further noted that "[t]his is in keeping with the knowledge that highly activated IFNγ+ cells tend to be short-lived…" (page 659). Taken together, the Hsieh et al. reference provides a study of a limited scope, and their results appear to show discrepancies from earlier published reports. Based solely on the data in the cited reference, one of skill in the art cannot reasonably draw a general inference or conclusion as to the effectiveness of CpG.

The Examiner also cited Manish et al. (2004). It is noted that the Examiner actually meant "Rauthan et al." (Manish Rauthan, Rupinderjeet Kaur, Mohan Babu Appaiahgari and Sudhanshu Vrati; 2004, Microbes & Infection 6(14): 1305-11), which is referred to hereafter as Rauthan et al. The Examiner cited Rauthan et al. to support his position that "[t]he prior art is unpredictable and teaches that many putative ISS elements do not function in the manner desired and often fail to facilitate immune responses to the immunogen of interest." Rauthan et al. examined oral immunization of mice with Japanese encephalitis virus (JEV) envelope protein synthesized in Escherichia coli. The authors found that mice immunized with recombinant JEV envelope protein made high-titered anti-E and anti-JEV antibodies. The authors further found that mice immunized with the same antigen but "along with [an] ODN adjuvant" produced "higher antibody titers" and that "these were predominantly IgG2a type" (Abstract). While the authors noted that these antibodies "failed to neutralize JEV activity in vitro," they concluded that the "results indicate that JEV E protein delivered orally to mice together with ODN generate both humoral and cellular immune responses to JEV, and these were of the Th1 type" (Abstract).

Presumably, the Examiner has focused on the above-noted observation of Rauthan et al. that "these antibodies...failed to neutralize JEV activity in vitro" in making his conclusion that immunostimulatory CpG oligonucleotides "often fail to *facilitate immune responses* to the immunogen of interest" (Emphasis added). Contrary to the Examiner's assertion, Applicant respectfully contends that the results presented in the cited reference by Rauthan et al. in fact clearly demonstrate that CpG *did* facilitate antigen-specific immune responses. The authors only noted that under the particular condition employed in their experiments, the CpG ODN that they used did not "neutralize JEV activity in vitro" to "protect the mice against lethal JEV challenge." However, the authors noted that the CpG ODN produced "higher antibody titers" and "these were predominantly IgG2a type." Applicant asserts that these are in fact "antigen-specific immune responses." The failure of the antibodies to neutralize JEV is likely to be do to the selection of antigen. Since antibodies arise in response to conformational epitopes, this finding indicates that the authors selected the wrong form of antigen, not that the adjuvants didn't work. The demonstrate that the CpG oligonucleotides did in fact work. The instant claims are directed to methods of "inducing an

antigen specific immune response in a subject." The teaching of the Rauthan reference is therefore consistent with the claimed invention.

The Examiner next cited Weiner (J. Leukocyte Biol., 2000), stating that "Weiner notes that 'flanking nucleotide sequences have unpredictable effects of the immune activities of CpG-ODN'"(Office Action page 3).

Respectfully, this is a mischaracterization. Applicant does not refute that flanking sequences may impact the immunostimulatory properties of CpG ODNs. Nevertheless, they are still immunostimulatory. In fact, the Weiner reference in accordance alludes to this notion as reproduced below (page 458, left column; citations omitted):

> A variety of cell populations are activated by CpG ODN, and CpG ODN with different sequences vary in their ability to activate various cell populations. There is also variability from species to species. This makes definition of the immunological effects of a specific CpG ODN complex. Despite this heterogeneity, a number of patterns of cellular activation appear to be emerging, which is allowing us to designate various classes of CpG ODN. Some CpG ODN induce significant activation of APCs (monocytes, dendritic cells), NK cells, and production of IFN-α, but have little impact on B cells. This class of ODN has recently been designated as "CpG-α" Other CpG ODN activate APCs and NK cells, but induce little IFN-α. These CpG ODN are potent activators of B cells. These are designated "CpG-ß." The rules related to which CpG ODN will be CpG-α and which will be CpG-ß are only now being worked out. What is clear is that the CpG motifs are not the only sequences that are relevant and that the nucleotides preceding and following the CpG motifs can have a significant impact on the immune effects of the ODN.

Thus, Weiner provides a discussion regarding different classes of immunostimulatory CpG ODNs. But the point is that, even though flanking sequences and/or the type of the backbone modifications of a CpG ODN may affect the immunostimulatory profile, the CpG ODN is in principle still immunostimulatory. Thus, "variability" and "heterogeneity" discussed in the cited reference refer to different degrees and/or different types of immunostimulatory responses, not "unpredictability" of their *immunostimulatory nature* as implied by the Examiner. Based on this, the Examiner concluded that biological effects of CpG containing oligonucleotides are "highly unpredictable" (Office Action page 4). Again, Applicant does not refute that certain structural modifications, such as backbone modification, may have an effect on the function of a CpG containing immunostimulatory oligonucleotides, in particular on the stability of the molecule *in vivo*. These factors relate to an issue of optimization and formulation. It does not necessarily

follow that the CpG oligonucleotides are "unpredictable" as to their immunostimulatory nature. Thus, these secondary factors that contribute to optimization and possibly efficacy of an immunostimulatory oligonucleotide do not reasonably refute the instantly claimed invention.

Consistent with this notion, the Pisetsky reference (Immunologic Res., 1999) cited by the Examiner at the outset teaches that "[immunostimulatory] activities result from short-sequence motifs...which are called CpG motifs or immunostimulatory sequences (ISS), have the general structure of two 5' purines, an unmethylated CpG dinucleotide, and two 3' pyrimidines." Based on this fundamental premise, the author further discusses additional structural features, such as neighboring sequences, e.g., the context in which CpG motifs in genomic DNA are present, and backbone modifications, that can *modulate* the immunostimulatory properties. In the context of backbone modifications, the author notes that different backbone modifications (e.g., PO and PS) can influence immunostimulatory properties of CpG ODNs. The cited reference teaches that "[s]everal lines of evidence, however, suggest caution in the use of PS compounds to explore the mechanism of action of immunostimulatory DNA and its structure-function relationships" (page 43, left column). However, Applicant wishes to point out that the "caution" referred to is made against treating PO oligos and PS oligos completely the same way, *not* against the notion that PS-modified CpG oligos are immunostimulatory. Indeed, the sentence that precedes the above-cited statement reads as follows: "In view of potency of PS oligos and their obvious structural similarity to PO oligos, many investigators have treated these compounds as equivalent."

Notably, on page 42 of the cited reference, the author stated that, "[i]ndeed, CpG DNA has many potential therapeutic uses such as adjuvants for protein vaccines as well as immunomodulatory agents to induce the shirt of the Th1:Th2 cell balance via induction of IL-12 and IFN-γ." This suggests that, despite his own "caution," the author in fact believes that CpG immunostimulatory oligos are suitable for therapeutic applications. In this regard, it may be reasonably interpreted that the author's "caution" regarding the PS effects, as discussed above, may extend to the notion that for clinical purposes in particular these "variations" must be taken into account in developing safe and effective pharmaceutical compositions comprising a CpG immunostimulatory oligonucleotide.

Granted, this in itself does not refute the claimed invention. Applicant respectfully disagrees with the implied notion that such variations amount to unpredictability or undue experimentation. Variations associated with therapeutics amongst species, or in some cases amongst individuals of the same species, are to be expected. Like any therapeutic reagent, therefore, it is reasonably expected that optimal effects of the immunostimulatory oligonucleotides of the instant invention can depend on various factors, as noted by the Examiner, such as various modes of administration. Applicant does not dispute the notion. In fact, even with an FDA-approved drug, a certain degree of optimization is required. That in itself, however, does not render the claimed invention unpatentable. Chapter 2100 of the MPEP states, "An applicant's specification must enable a person skilled in the art to make and use the claimed invention without undue experimentation. The fact that experimentation is complex, however, will not make it undue if a person of skill in the art typically engages in such complex experimentation." Given the amount of information provided regarding CpG nucleic acids, the skilled artisan would have no trouble implementing the claimed invention as an adjuvant. That is, the skilled artisan would know how to make and prepare a composition comprising an unmethylated nucleic acid as described in the specification as filed. In addition, the skilled artisan would know how to optimize the same, based on the various parameters as presented in the examples to assay immune responses in a subject.

Applicant further wishes to note that case law is clear in that issues such as optimization and safety of a therapeutic agent are to be properly left to the FDA (See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]."). In the instant case, Applicant provided adequate working examples, not merely a prophetic example, to demonstrate immunostimulatory effects of the CpG oligonucleotides of the present invention, and the evidence as a whole should teach one skilled in the art how to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973). The evidence provided by applicant need not be *conclusive* but merely *convincing* to one skilled in the art.

Thus, what is being alleged by the Examiner as "unpredictable" is not the immunostimulatory nature of the claimed invention *per se*, but with respect to the aspect of

optimization and safety, e.g., the degree of efficacy, optimal administration mode, etc., which, again, ultimately relates to a regulatory issue that falls within a territory of the Food and Drug Administration, not to the statutory standards of patentability as set forth in 35 U.S.C. In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement. Applicant wishes to reiterate that in any of the cited references, the immunostimulatory nature of CpG oligonucleotides *per se* is not questioned.

In sum, Applicant submits that the above-cited references do not contradict the present invention. To the contrary, the cited papers, including those published years after the filing date, continue to support the view that CpG oligonucleotides should be advanced through clinical trials for use as therapeutic agents for purposes of preventing and/or treating medical conditions, such as vaccines. One of ordinary skill in the art would have believed, based on the disclosure of the application, that CpG oligonucleotides would be well suited for the claimed use.

Finally, the Examiner cited Vollmer et al. (Antisense & Nuc Acid., 2002) to support the position that the state of the art regarding immunostimulatory CpG oligonucleotides indicated the art is unpredictable. Applicant respectfully contends that Vollmer et al. is not relevant to the claimed invention. Briefly, Vollmer et al. identified that certain motifs that do not contain a CpG motif can also be immunostimulatory, e.g., activate human leukocytes. More specifically, the authors observed that non-CpG ODNs rich in thymidine or ODNs with methylated CpG motifs have length-dependent immunostimulatory effects in certain contexts. Since these results do not negate or contradict the instantly claimed invention, the cited reference neither supports nor refute the Examiner's position with respect to immunostimulatory CpG oligonucleotides. Thus, the Vollmer reference does not support the alleged lack of enablement in the instant case.

The Examiner further argued that "the claims are of considerable breadth and are not fully supported by the disclosure." Applicant respectfully disagrees. The Examiner's position is that because "[t]he broadest claims are not limited to any particular CpG-ODN or immune stimulating adjuvant or immunogen...the claims literally encompass tens-of-thousands of permutations," the

Examiner concludes that therefore it "would clearly require undue experimentation" (Office Action, pages 3-4).

Applicant respectfully submits that just because the claimed genus is a large one, that in itself does not make the disclosure non-enabling. As is clear from the references cited by the Examiner, and hundreds of other articles published in peer-reviewed journals since its discovery, the unmethylated CpG dinucleotide motif is known to be and accepted as immunostimulatory. Due in part to its relative simplicity of the basic structural requirement to confer immunostimulatory effects, naturally, the broad claims indeed encompass a large number of embodiments. That in itself is not a valid basis for denying patentability. Applicant has presented sufficient information and believes that it correlates with the scope of the claimed invention. Applicant contends that a correlation between CpG nucleic acids and their use in a combination of adjuvants is disclosed and thus the full scope of the instant claims is enabled. MPEP section 2164.02 states that:

> "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
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> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)"

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In *Wands* the court observed that "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." Id. Contrary to the Examiner's assertion that there is a "lack of guidance," Applicant respectfully contends that adequate guidance is provided to the direction in which the experimentation should

proceed such that those skilled in the art can use the claimed invention for inducing an antigen-specific immune response using an immunostimulatory CpG oligonucleotide for a combination adjuvant.

Based upon the foregoing, Applicant respectfully submits that the claimed invention is enabled. Accordingly, it is respectfully requested that the rejection made under 35 U.S.C. § 112 be reconsidered and withdrawn. Applicant believes that the instant claims are in an allowable condition. Favorable response is earnestly solicited.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, please charge any deficiency to Deposit Account No. 23/2825.

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Respectfully submitted,

By _____

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